

## Overview

### Useful For

Confirmation of suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis

Identification of gene mutations contributing to pancreatitis in an individual or family

Identification of gene mutations to allow for predictive and diagnostic testing in family members

### Genetics Test Information

This test includes Sanger sequencing to evaluate for mutations in the *PRSS1* gene, next-generation sequencing to evaluate for mutations in the *CFTR*, *CTRC*, and *SPINK1* genes, and multiplex ligation-dependent probe amplification for the detection of large deletions and duplications within the *CFTR* gene.

### Highlights

This test evaluates for mutations within the 4 most common genes associated with susceptibility to chronic pancreatitis: *PRSS1*, *CFTR*, *CTRC*, and *SPINK1*

This assay provides diagnostic confirmation of hereditary pancreatitis or identification of gene mutations contributing to pancreatitis in an individual or family

### Special Instructions

- [Molecular Genetics: Congenital Inherited Diseases Patient Information](#)
- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

### Specimen Required

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Specimen Type:** Whole blood

**Container/Tube:**

**Preferred:** Lavender top (EDTA) or yellow top (ACD)

**Acceptable:** Any anticoagulant

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send specimen in original tube.

**Additional Information:** To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

**Forms**

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing-Spanish](#) (T826)

2. [Molecular Genetics: Congenital Inherited Diseases Patient Information](#) (T521) in Special Instructions

3. If not ordering electronically, complete, print, and send a [Gastroenterology and Hepatology Client Test Request](#) (T728) with the specimen.

**Specimen Minimum Volume**

1 mL

**Reject Due To**

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

**Clinical and Interpretive**

**Clinical Information**

[Hereditary pancreatitis \(HP\) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations. Mutations in several genes, including PRSS1, CFTR, CTSC, and SPINK1](#) have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with *PRSS1*, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression.

***PRSS1:***

The most common monogenic cause of HP is the presence of a mutation in the cationic trypsinogen (*PRSS1*) gene. Mutations in the *PRSS1* gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative *PRSS1* mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, *PRSS1* mutations are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced or tropical pancreatitis. Although several mutations have been identified, the R122H, N29I, and A16V mutations are the most common disease-causing mutations in *PRSS1* associated with HP. Data suggests that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%.

***SPINK1:***

Biallelic mutations in the *SPINK1* gene have been associated with increased susceptibility to chronic pancreatitis especially in families without *PRSS1* mutations; however, it is unknown if biallelic mutations alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous *SPINK1* mutations appear to modify disease severity when observed in combination with mutations in other genes. Unlike *PRSS1* mutations, *SPINK1* mutations have been associated with alcohol-induced and tropical pancreatitis.

***CFTR:***

Pancreatitis is a known manifestation of an atypical *CFTR*-related disorder in which 2 mutations in the *CFTR* gene are identified. However, *CFTR* mutations can also co-occur with mutations in *CTRC*, *SPINK1*, or *CASR* to confer pancreatitis disease susceptibility. When observed in the context of a *SPINK1* mutation, for example, heterozygous mutations in *CFTR* are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population.

***CTRC:***

Mutations in *CTRC* have been observed in individuals with chronic pancreatitis in association with other risk factors such as mutations in *CFTR* or *SPINK1* or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of *CTRC* mutations in the context of other risk factors as opposed to *CTRC* mutations alone.

**Reference Values**

An interpretive report will be provided.

**Interpretation**

All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Cautions**

Some individuals with a diagnosis of hereditary pancreatitis and/or involvement of the genes tested may have a mutation that is not identified by this method (eg, large genomic deletions or duplications, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of a diagnosis of hereditary pancreatitis or susceptibility to pancreatitis. For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene mutation in an affected family member.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in

our interpretation of results may occur if information given is inaccurate or incomplete.

Technical limitations:

In some cases, DNA variants of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In addition to disease-related probes, the multiplex ligation-dependent probe amplification (MLPA) technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Evaluation tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently unvalidated.

Unless reported or predicted to cause disease, alterations in protein coding genes that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic alterations or variants of uncertain significance that have been previously detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

## Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015 May;17(5):405-424
2. Raphael KL, Willingham FF: Hereditary pancreatitis: current perspectives. *Clin Exp Gastroenterol*. 2016 Jul 26;9:197-207
3. Solomon S, Whitcomb DC: Genetics of pancreatitis: an update for clinicians and genetic counselors. *Curr Gastroenterol Rep* 2012;14(2):112-117
4. Ellis I: Genetic counseling for hereditary pancreatitis-the role of molecular genetics testing for the cationic trypsinogen gene, cystic fibrosis and serine protease inhibitor Kazal type 1. *Gastroenterol Clin North Am* 2004;33:839-854
5. Pancreatitis Overview. In *GeneReviews-NCBI Bookshelf*. 2014 Mar 13. Edited by RA Pagon, MP Adam, HH Ardinger, et al: University of Washington,. Seattle WA. 1993-2018. Accessed January 2019. Available at URL: <http://www.ncbi.nlm.nih.gov/books/NBK190101/>

## Performance

### Method Description

Next-generation sequencing and/or Sanger sequencing is used to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *PRSS1*, *CFTR*, *CTRC*, and *SPINK1* genes. Sequencing of genomic regions encompassing select clinically relevant intronic mutations within the *CFTR* gene is also performed. Additionally, gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications in the *CFTR* gene. Sanger sequencing is used to confirm alterations detected by next-generation sequencing when appropriate. (Unpublished Mayo method)

### PDF Report

No

### Day(s) and Time(s) Test Performed

Performed weekly; Varies

### Analytic Time

14 days

### Maximum Laboratory Time

20 days

### Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

### Performing Laboratory Location

Rochester

## Fees and Codes

### Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

### Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

### CPT Code Information

81222

81223

81404 x2

81405

### LOINC® Information



---

Test ID	Test Order Name	Order LOINC Value
HPPAN	Hereditary Pancreatitis Panel	In Process

Result ID	Test Result Name	Result LOINC Value
52581	Result Summary	50397-9
52582	Result	82939-0
52583	Interpretation	69047-9
52584	Additional Information	48767-8
52585	Specimen	31208-2
52586	Source	31208-2
52587	Released By	18771-6